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     (FILE 'HOME' ENTERED AT 17:58:34 ON 22 JUL 2003)

     FILE 'CAPLUS' ENTERED AT 17:59:26 ON 22 JUL 2003

     FILE 'USPATFULL' ENTERED AT 18:30:56 ON 22 JUL 2003
L1          238 S ((GRANULE OR MICROGRANULE OR MICROSPHERES OR NANOSPHERES) AND
L2           58 S L1 AND (OIL-IN-WATER)
L3           12 S L2 AND POLYLACTIDE?

=> d bib,kwic 1-3,5,8-12

L3   ANSWER 1 OF 12  USPATFULL on STN
```

Full Text | Citing References

AN 2003:136818 USPATFULL
TI Methods of spray drying pharmaceutical compositions
IN Tarara, Thomas E., San Diego, CA, United States
Weers, Jeffry G., San Diego, CA, United States
Kabalnov, Alexey, Corvallis, OR, United States
Schutt, Ernest G., San Diego, CA, United States
Dellamary, Luis A., San Marcos, CA, United States
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6565885 B1 20030520
AI US 1998-219736 19981222 (9)
RLI Continuation of Ser. No. WO 1998-US20602, filed on 29 Sep 1998
Continuation-in-part of Ser. No. US 1998-133848, filed on 14 Aug 1998, now abandoned Continuation-in-part of Ser. No. US 1998-106932, filed on 29 Jun 1998, now abandoned
PRAI US 1997-60337P 19970929 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Haghighatian, M.
LREP Rafa, Michael J., Cagan, Felissa H.
CLMN Number of Claims: 104
ECL Exemplary Claim: 1
DRWN 19 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 3817
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as discussed in more detail below, surfactants comprising the structural matrix may also be useful in the formation of precursor **oil-in-water** emulsions (i.e. spray drying feed stock) used during processing to form the perforated microstructures.

DETD . . . matrix defining the perforated microstructure optionally comprises synthetic or natural polymers or combinations thereof. In this respect useful polymers comprise **polylactides**, **polylactide**-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin,. . .

DETD In selected embodiments an **oil-in-water** emulsion is then formed in a separate vessel. The oil employed is preferably a fluorocarbon (e.g., perfluorooctyl bromide, perfluorodecalin) which. . .

CLM What is claimed is:

11. The method of claim 1 wherein said collected perforated microstructures comprise hollow porous **microspheres**.

16. The method of claims 1 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary. . . or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, DNA, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

. . . of claim 1 wherein the feed stock further comprises a natural or synthetic polymer selected from the group consisting of **polylactides**, **polylactide**-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides, hyaluronic acid, and proteins.

59. The method of claim 56 wherein said collected particulates comprise hollow porous **microspheres**.

64. The method of claim 38 wherein the feed stock further comprises a natural or synthetic polymer selected from the group consisting of **polylactides**, **polylactide**-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides, hyaluronic acid, and proteins.

. . . or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, DNA, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

86. The method of claim 73 wherein said perforated microstructures comprise hollow porous **microspheres**.

90. The method of claim 72 wherein the feed stock further comprises a natural or synthetic polymer selected from the group consisting of **polylactides**, **polylactide**-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides, hyaluronic acid, and proteins.

. . . or antagonists, antihistamines, antiinflanmatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, DNA, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

98. The method of claim 97 wherein the perforated microstructures comprise hollow and porous **microspheres**.

101. The method of claim 100 wherein the perforated microstructures comprise hollow and porous **microspheres**.

104. The method of claim 103 wherein the perforated microstructures comprise hollow and porous **microspheres**.

L3 ANSWER 2 OF 12 USPATFULL on STN

Full Text | Citing References

AN 2003:64338 USPATFULL
TI Oral dosage form comprising a therapeutic agent and an adverse-effect agent
IN Wright, Curtis, IV, Norwalk, CT, UNITED STATES
Carpanzano, Anthony E., Sherman, CT, UNITED STATES
PI US 2003044458 A1 20030306
AI US 2002-208817 A1 20020801 (10)
PRAI US 2001-309791P 20010806 (60)
DT Utility
FS APPLICATION
LREP PENNIE & EDMONDS LLP, 1667 K STREET NW, SUITE 1000, WASHINGTON, DC, 20006
CLMN Number of Claims: 79
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 1562
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . a coating that is substantially insoluble in the gastrointestinal tract also include, but not limited to, poly(lactic/glycolic acid) ("PLGA") copolymers, **polylactides**, polyglycolides, polyanhydrides, polyorthoesters, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polyesters, polydioxanone, polygluconate, polylactic-acid polyethylene oxide copolymers, poly(hydroxybutyrate), polyphosphoesters, and mixtures thereof.

DETD . . . sustained-release coating comprises a water-insoluble material, such as a wax or a wax-like substance, fatty alcohol, shellac, zein, hydrogenated vegetable **oil**, **water** insoluble cellulose, polymer of acrylic and/or methacrylic acid, or any other slowly digestible or dissolvable solid known in the art.. . . .

DETD [0072] Other polymers suitable for use in the invention include, but are not limited to, hydroxyalkylcelluloses; poly(lactic/glycolic acid) ("PLGA"); **polylactide**; polyglycolide; polyanhydrides; polyorthoesters; polycaprolactone; polyphosphazenes; polysaccharides; proteinaceous polymers; polyesters; polydioxanone; polygluconate; polylactic-acid polyethylene oxide copolymers; poly(hydroxybutyrate) polyphosphoesters; or mixtures thereof.

CLM What is claimed is:

. . . oral dosage form of claim 1, wherein the first composition and the second composition are in the form of powders, **granules**, or beads contained within a capsule.

. . . The oral dosage form of claim 1, wherein the first composition and the second composition are in the form of **granules** or a powder dispersed in a pharmaceutically acceptable matrix.

. . . 13, wherein the sustained-release coating is selected from the group consisting of a wax, fatty alcohol, shellac, zein, hydrogenated vegetable **oil**, **water** insoluble cellulose, polymers of acrylic acid, polymers of methacrylic acid, copolymers of acrylic acid and methacrylic acid, and mixtures thereof.

. . .

. . . colony stimulating factor, parathyroid hormone, luteinising hormone releasing hormone and analogues thereof, atrial natriuretic factor, vasopressin, desmopressin, calcitonin gene related **peptide**, and analgesics.

. . . oral dosage form of claim 37, wherein the first composition and the second composition are in the form of powders, **granules**, or beads contained within a capsule.

. . . The oral dosage form of claim 37, wherein the first composition and the second composition are in the form of **granules** or a powder dispersed in a pharmaceutically acceptable matrix.

. . . 51, wherein the sustained-release coating is selected from the group consisting of a wax, fatty alcohol, shellac, zein, hydrogenated vegetable **oil**, **water** insoluble cellulose, polymers of acrylic acid, polymers of methacrylic acid, copolymers of acrylic acid and methacrylic acid, and mixtures thereof.

. . .

. . . colony stimulating factor, parathyroid hormone, luteinising hormone releasing hormone and analogues thereof, atrial natriuretic factor, vasopressin, desmopressin, calcitonin gene related **peptide**, and analgesics.

L3 ANSWER 3 OF 12 USPATFULL on STN

Full Text | Citing References

AN 2003:37200 USPATFULL

TI Injectable sustained release pharmaceutical composition and processes for preparing the same

IN Lee, Hee-Yong, Iksan-shi, KOREA, REPUBLIC OF
Lee, Hye-suk, Iksan-shi, KOREA, REPUBLIC OF
Kim, Jung-Soo, Jeonju-shi, KOREA, REPUBLIC OF
Kim, Sang-Beom, Kunsan-shi, KOREA, REPUBLIC OF
Lee, Ji-Suk, Kunsan-shi, KOREA, REPUBLIC OF
Choi, Ho-Il, Taejon, KOREA, REPUBLIC OF
Chang, Seung-Gu, Tajeon, KOREA, REPUBLIC OF

PI US 2003026844 A1 20030206
AI US 2002-18870 A1 20020418 (10)
WO 2001-KR462 20010322
PRAI KR 2000-20484 20000418
KR 2000-49344 20000824
DT Utility
FS APPLICATION
LREP Eric B Meyertons, Conley, Rose, & Tayon, P.C., P O Box 398, Austin, TX, 78767
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 9 Drawing Page(s)
LN.CNT 891
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . microspheres in drug delivery, Crit. Rev. Ther. Drug Carrier Syst., 12, 1-99 (1995)]. Among the biodegradable polymers, aliphatic polyesters including **polylactides**, polyglycolides and their copolymers have been mostly investigated due to the great biocompatibility and variable time range of biodegradability dependent. . .

SUMM . . . Rel., 28, 25-42 (1997), U.S. Pat. Nos. 4,818,542, 5,942,253]. Due to the hydrophilic nature of most protein drugs, water in **oil** in **water** (w/o/w) double emulsion solvent evaporation technique is frequently used for encapsulating protein into a biodegradable polymeric matrix. In this process,. . .

DETD . . . Another aspect of the present invention is to provide said processes, wherein said biodegradable polymer is one or more of **polylactides**, polyglycolides, poly(lactide-co-glycolide)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and. . .

DETD . . . Pat. Nos. 3,960,757, 4,818,542, 5,160,745, 5,830,493, 5,916,597, 5,942,241. In particular, preferred polymers are biodegradable polymers including synthetic polymers such as **polylactides**, polyglycolides, poly(lactide-co-glycolide)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and. . .

DETD . . . of ionic groups into biodegradable polymers can be carried out by conventional chemical reactions. For example, aliphatic polyesters such as **polylactides**, polyglycolides, and poly(lactide-co-glycolide)s may have cationic functional groups by modification of hydroxyl or carboxyl groups therein into amino groups.

DETD . . . aspects are well described in U.S. Pat. Nos. 3,523,906, 4,652,441, 5,288,502, 4,606,940, 5,271,961, 5,518,709, 5,019,400, and 5,043,280. Particularly, water in **oil** in **water** (w/o/w) double emulsion solvent extraction and evaporation method is preferred. In this method, fine water droplets in the primary emulsion. . .

CLM What is claimed is:

1. A process to prepare an injectable sustained release pharmaceutical composition comprising a step to prepare biodegradable porous **microspheres** having accessible ionic functional groups, a step to incorporate a biopharmaceutical into the **microspheres** through ionic interaction by suspending or equilibrating the **microspheres** in a solution containing the biopharmaceutical and a step to recover and freeze-dry the biopharmaceutical-incorporated **microspheres**.

. . . 2. The process of claim 1, wherein the composition is prepared by incorporation of a cationic biopharrnaceutical into biodegradable porous

microspheres having anionic functional groups and wherein the pH of incorporation solution is lower than the pI of the biopharmaceutical.

. . . 3. The process of claim 1, wherein the composition is prepared by incorporation of an anionic biopharmaceutical into biodegradable porous **microspheres** having cationic functional groups and wherein the pH of incorporation solution is higher than the pI of the biopharmaceutical.

5. The process of claim 1-3, wherein said biodegradable polymer is one or more of **polylactides**, polyglycolides, poly(lactide-co-glycolide)s, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, poly(amino acids), polyolthoesters, polyacetyls, polycyanoacrylates, polyetheresters, poly(dioxanone)s, poly(alkylene alkylate)s, copolymers of polyethylene glycol and. . .

7. The process according to any of the claims 2, 4, 5, wherein said biodegradable porous **microspheres** having anionic functional groups are prepared from the blends of anionic surfactant and/or biocompatible materials having anionic functional group with. . .

10. The process according to any of the claims 3, 4, 5, wherein said biodegradable porous **microspheres** having cationic functional groups are prepared from the blends of cationic surfactant or biocompatible materials having cationic functional group with. . .

. . . said biopharmaceutical is selected from the group consisting of growth hormones, interferons, colony stimulating factors, interleukins, macrophage activating factors, macrophage **peptides**, B cell factors, T cell factors, protein A, suppressive factor of allergy, suppressor factors, cytotoxic glycoprotein, immunocytotoxic agents, immunotoxins, immunotherapeutic. . . platelet derived growth factor, osteogenic growth factors, atrial naturetic factor, auriculin, atriopeptin, bone morphogenetic protein, calcitonin, calcitonin precursor, calcitonin gene-related **peptide**, cartilage inducing factor, connective tissue activator protein, fertility hormones (follicle stimulating hormone, leutinizing hormone, human chorionic gonadotropin), growth hormone releasing. . . hormone, parathyroid hormone inhibitors, relaxin, secretin, somatomedin C, insulin-like growth factors, inhibin, adrenocorticotrophic hormone, glucagons, vasoactive intestinal polypeptide, gastric inhibitory **peptide**, motilin, cholecystolinin, pancreatic polypeptide, gastrin releasing **peptide**, corticotropin releasing factor, thyroid stimulating hormone, vaccine antigens of, and anti-infective antibodies to, bacterial or viral or other infectious organisms. . .

13. The process according to any of the claims 1-3, wherein said biodegradable porous **microspheres** having ionic functional groups are prepared by a method selected from solvent extraction or evaporation in aqueous or organic phase,. . .

14. The process according to any of the claims 1-3, wherein porosity of said biodegradable porous **microspheres** having ionic functional groups is intended to be increased by addition of gas forming agents or salts such as sodium. . .

15. The process according to any of the claims 1-3, wherein said biodegradable porous **microspheres** having ionic functional groups are prepared by co-addition of acidifying agents such as lactic acid, glycolic acid, tartaric acid, citric. . .

. . . 16. The process according to any of the claims 1-3, wherein the incorporation of a biopharmaceutical into said biodegradable porous **microspheres** having ionic functional groups are performed in an aqueous buffer solution, where the pH of the buffer is from 3.0. . .

20. The process according to any of the claims 1-3, wherein the size of the **microspheres** is within the range from 0.01 to 500 μm.

L3 ANSWER 5 OF 12 USPATFULL on STN

Full Text | Citing References

AN 2002:202150 USPATFULL

TI Stabilized bioactive preparations and methods of use

IN Dellamary, Luis A., San Marcos, CA, United States
Tarara, Thomas E., San Diego, CA, United States
Kabalnov, Alexey, Corvallis, OR, United States
Weers, Jeffry G., San Diego, CA, United States
Schutt, Ernest G., San Diego, CA, United States
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6433040 B1 20020813
AI US 1998-218209 19981222 (9)
RLI Continuation of Ser. No. WO 1998-US20613, filed on 29 Sep 1998 Continuation-in-part of Ser. No. US 1998-133848, filed on 14 Aug 1998, now abandoned Continuation-in-part of Ser. No. US 1998-106932, filed on 29 Jun 1998, now abandoned
PRAI US 1997-60337P 19970929 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Szekely, Peter
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2587
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as discussed in more detail below, surfactants comprising the porous particles may also be useful in the formation of precursor **oil-in-water** emulsions (i.e. spray drying feed stock) used during processing to form the structural matrix.

DETD . . . matrix defining the perforated microstructure optionally comprises synthetic or natural polymers or combinations thereof In this respect useful polymers comprise **polylactides**, **polylactide-glycolides**, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin,. . .

DETD In selected embodiments an **oil-in-water** emulsion is then formed in a separate vessel. The oil employed is preferably a fluorocarbon (e.g., perfluorooctyl bromide, perfluorodecalin) which. . .

CLM What is claimed is:

5. The method of claim 1wherein said perforated microstructures further comprise hollow porous **microspheres**.

6. The method of claim 1 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary. . . antagonists, antihistamines, anti-inflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

15. The method of claim 10 wherein said perforated microstructures further comprise hollow porous **microspheres**.

16. The method of claim 10 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary. . . antagonists, antihistamines, anti-inflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

24. The dispersion of claim 18 wherein said perforated microstructures further comprise hollow porous **microspheres**.

25. The dispersion of claim 18 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary. . . antagonists, antihistamines, anti-inflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

use of surf-s polylactide ⊖; no charged

L3 ANSWER 8 OF 12 USPATFULL on STN

Full Text | Citing References

AN 2001:190709 USPATFULL
TI Stabilized preparations for use in metered dose inhalers
IN Weers, Jeffry G., San Diego, CA, United States
Schutt, Ernest G., San Diego, CA, United States
Dellamary, Luis A., San Marcos, CA, United States
Tarara, Thomas E., San Diego, CA, United States
Kabalnov, Alexey, Corvallis, OR, United States
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6309623 B1 20011030
AI US 1998-218212 19981222 (9)
RLI Continuation of Ser. No. WO 1998-US20615, filed on 29 Sep 1998 Continuation-in-part of Ser. No. US 1998-133848, filed on 14 Aúg 1998, now abandoned Continuation-in-part of Ser. No. US 1998-106932, filed on 29 Jun 1998, now abandoned
PRAI US 1997-60337P 19970929 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Bawa, Raj
LREP Rafa, Michael J., Cagan, Felissa H.
CLMN Number of Claims: 93
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2644
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as discussed in more detail below, surfactants comprising the porous particles may also be useful in the formation of precursor **oil-in-water** emulsions (i.e. spray drying feed stock) used during processing to form the structural matrix.

DETD . . . matrix defining the perforated microstructure optionally comprises synthetic or natural polymers or combinations thereof In this respect, useful polymers comprise **polylactides**, **polylactide**-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin,. . .

DETD In selected embodiments an **oil-in-water** emulsion is then formed in a separate vessel. The oil employed is preferably a fluorocarbon (e.g., perfluorooctyl bromide, perfluorodecalin) which. . .

CLM What is claimed is:

19. The stable respiratory dispersion of claim 1 wherein said perforated microstructures comprise hollow porous **microspheres**.

20. The stable respiratory dispersion of claim 19 wherein the **microspheres** comprise a surfactant.

. . . antagonists, antihistamine, antiinflammatories, antineoplastics, antocholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides**, and combinations thereof.

. . . stable respiratory dispersion of claim 1 wherein said bioactive agents are selected from the group consisting of steroids, bronchodilators and **peptides**.

32. The method of claim 30 further comprising the step of spray drying an **oil-in-water** emulsion to provide said perforated microstructures wherein the disperse phase of said emulsion comprises a fluorochemical.

47. The method of claim 30 wherein said perforated microstructures comprise hollow **microspheres**.

52. The method of claim 30 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary. . . antagonists, antihistamines, antiinflammatories, antineoplastics, antcholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

67. The method of claim 53 wherein said perforated microstructures comprise hollow porous **microspheres**.

71. The method of claim 53 wherein said perforated microstructures comprise a bioactive agent selected from the group consisting of. . . antagonists, antihistamines, antiinflammatories, antineoplastics, antcholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

83. The respiratory dispersion of claim 82 wherein said perforated microstructures comprise hollow porous **microspheres**.

84. The respiratory dispersion of claim 83 wherein said hollow porous **microspheres** have a mean aerodynamic diameter between 0.5 to 5 μm.

. . . antagonists, antihistamines, antiinflammatories, antineoplastics, antcholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, **peptides** and combinations thereof.

L3 ANSWER 9 OF 12 USPATFULL on STN

Full Text | Citing References

AN 2001:125488 USPATFULL
TI Encapsulation of water soluble peptides
IN Ignatious, Francis X., Exton, PA, United States
PA Societe de Conseils de Recherches et d'Applications Scientifiques, SAS, Paris, France (non-U.S. corporation)
PI US 6270700 B1 20010807
AI US 1999-357453 19990720 (9)
PRAI US 1998-93914P 19980723 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Morrill, Brian R., Feeney, Alan F., Conway, John D.
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 783
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a process for preparing biodegradable microspheres and or nanospheres using an **oil-in-water** process for the controlled release of bioactive peptides.
SUMM This invention relates to a process for preparing biodegradable microspheres and/or nanospheres using an **oil-in-water** process, which microspheres and nanospheres can be used for the controlled release of bioactive peptides.
SUMM . . . the solvent. When the polymer is dissolved in an organic medium and then emulsified in water, the process is called **oil-in-water** process (O/W). Water soluble peptides cannot be encapsulated by the O/W process, due to the partition of the water soluble. . . into the aqueous medium, resulting in low encapsulation efficiency. Higher encapsulation efficiencies were achieved by a more complex double emulsion water-in-**oil-in-water** (W/O/W) process (U.S. Pat. No. 5,271,945) or by using an oil-in-oil (O/O) process (EP 0330180 B1). The main drawback of. . .
SUMM A preferred process of any of the foregoing processes is where the

polymer is **polylactide**-co-glycolide, polycaprolactone or polyanhydride or a copolymer or blends thereof.

SUMM Preferred of the immediately foregoing process is where the polymer is **polylactide**-co-glycolide, polycaprolactone or polyanhydride or a copolymer or blends thereof and where the peptide is the LHRH analogue of the formula. . .

SUMM Polymers that can be used to form microspheres include bioerodible polymers such as polyesters (ex. **polylactides**, polyglycolides, polycaprolactone and copolymers and blends thereof), polycarbonates, polyorthoesters, polyacetals, polyanhydrides, their copolymers or blends, and non-bioerodible polymers such as. . .

SUMM Polymers that can be used to form microspheres include biodegradable polymers such as polyesters (ex. **polylactides**, polyglycolides, polycaprolactone and copolymers and blends thereof) polycarbonates, polyorthoesters, polyacetals, polyanhydrides, their copolymers or blends, and non-biodegradable polymers such as. . .

CLM What is claimed is:

1. A process for preparing polymer **microspheres** comprising a polymer and a **peptide**, which comprises the steps of: neutralizing a **peptide** salt with a weak base in an aqueous medium wherein said medium comprises a suspension of hydroxyapatite or a solution. . . suspension; dispersing the suspension in an aqueous solution of a surfactant; and evaporating the organic solvent to isolate the polymer **microspheres**.

2. A process according to claim 1, comprising the additional step of dissolving the **peptide** salt in a minimum of water before neutralizing the **peptide** salt.

9. A process according to claim 8, wherein the **peptide** is growth hormone releasing **peptide**, luteinizing hormone-releasing hormone, somatostatin, bombesin, gastrin releasing **peptide**, calcitonin, bradykinin, galanin, melanocyte stimulating hormone, growth hormone releasing factor, amylin, tachykinins, secretin, parathyroid hormone, enkephalin, endothelin, calcitonin gene releasing **peptide**, neuromedins, parathyroid hormone related protein, glucagon, neurotensin, adrenocorticothrophic hormone, **peptide** YY, glucagon releasing **peptide**, vasoactive intestinal **peptide**, pituitary adenylate cyclase activating **peptide**, motilin, substance P, neuropeptide Y, or TSH or an analogue or a fragment thereof or a pharmaceutically acceptable salt thereof.

. . .

10. A process according to claim 9, wherein the **peptide** is the LHRH analogue of the formula pyroGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2.

11. A process according to claim 10, wherein the polymer is **polylactide**-co-glycolide, polycaprolactone or polyanhydride or a copolymer or blends thereof.

12. A process according to claim 9, wherein the **peptide** is selected from the group of somatostatin analogues consisting of H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH_2, ##STR8## and ##STR9##

13. A process according to claim 12, wherein the polymer is **polylactide**-co-glycolide, polycaprolactone or polyanhydride or a copolymer or blends thereof.

L3 ANSWER 10 OF 12 USPATFULL on STN

Full Text | Claim References

AN 97:80981 USPATFULL

TI Preparation of peptide containing biodegradable microspheres by melt process

IN Cha, Younsik, Salt Lake City, UT, United States

Choi, Young Kweon, Salt Lake City, UT, United States
Pai, Chaul Min, Taejon, Korea, Republic of
PA Macromed, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 5665428 19970909
AI US 1995-547962 19951025 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Thorpe, North & Western, L.L.P.
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1205
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and spray congealing; (g) air suspension coating; and (h) pan coating. As exemplified in U.S. Pat. No. 4,652,441, a W/O/W (water/oil/water) double emulsion in-water drying process is a commonly used method for microencapsulation of water-soluble hydrophilic drugs such as peptides and. . .

SUMM . . . mingled in a molecular order. By using a co-solvent such as acetonitrile-water mixtures or glacial acetic acid for the oligomeric **polylactides** and various drugs including peptides and proteins, the active substance can be uniformly incorporated into the microspheres without loss of. . .

SUMM . . . average molecular weight of 5,000 as carriers for the continuous release of polypeptide drugs. The hydrophobic block component, such as **polylactide**, is biodegradable and the hydrophilic block component, such as polyethylene glycol, may or may not be biodegradable. Such copolymeric compositions. . .

SUMM The release of a polypeptide from a **polylactide** polymer is often preceded by a significant induction period, during which no polypeptide is released, or is polyphasic which comprises. . .

SUMM . . . is to copolymerize lactic acid with glycolic acid to form poly(lactide-glycolide) copolymers. Another is to mix a peptide encapsulated in **polylactide** polymer with the same peptide encapsulated in other polymers or copolymers. Both of these methods are difficult to control during. . .

SUMM . . . Pat. No. 5,330,768. This patent discloses degradable polymeric matrices prepared by the physical blending of biodegradable hydrophobic polymers, such as **polylactides**, with nonionic hydrophilic copolymers, such as surfactant block copolymers of polyethyleneoxide (PEO) and polypropyleneoxide (PPO). Protein or peptide drugs are. . . within a polymeric skeleton which provide for extended protein release and minimized initial protein burst as compared to the pure **polylactide** polymers. However, when polymer blends are prepared as microspheres, a modified solvent evaporation technique using double emulsion is employed which. . .

DETD These copolymers are biodegradable and biocompatible. Polyethylene glycol, **polylactide** and lactide/glycolide copolymers are approved by FDA for medical use. Thermoplastic biodegradable hydrogels, such as these, are considered to have. . .

DETD . . . peptide or protein drugs. Of more relevance is the size of the microparticles which are formed. When formed in an **oil** or **water** for purposes of injection the particle size will generally range from about 1 to 100 μm and when formed for. . .

CLM What is claimed is:
1. A process for preparing **microspheres** of an admixture of a biodegradable low melting point block copolymer and a water soluble and heat resistant **peptide**/protein drug, which comprises: (a) preparing a molten mixture of an effective amount of **peptide**/protein drug microparticles and a biodegradable block copolymer at a temperature above the melting temperature of said block copolymer; (b) dispersing. . . the temperature of said microdroplets in a cooling environment below the melting point of said block copolymer to form solid **microspheres**; and (d) separating said **microspheres** from said continuous fluid medium.

11. A process according to claim 6 wherein said **peptide**/protein drug is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, prolactin, luliberin or. . .

. . . 19 wherein said liquid is cooled below the melting point of said copolymer causing said molten mixture to harden into **microspheres** and separating said **microspheres** from said liquid.

21. A process according to claim 20 wherein said **microspheres** are separated from said liquid by means of centrifugation, filtration, or decantation.

. . . in a sterile environment at a temperature below the melting point of said copolymer and wherein the concentration of said **microspheres** in said oil is between about 10 to 50% w/v.

L3 ANSWER 11 OF 12 USPATFULL on STN

Full Text | Citing References

AN 97:49618 USPATFULL
TI Composition for the sustained and controlled release of medicamentous substances and a process for preparing the same
IN Orsolini, Piero, Martigny, Switzerland
Heimgartner, Frederic, Martigny, Switzerland
PA Asta Medica Ag, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5637568 19970610
AI US 1994-210097 19940316 (8)
RLI Continuation of Ser. No. US 1992-915490, filed on 16 Jul 1992, now abandoned
PRAI CH 1991-2178 19910722
DT Utility
FS Granted
EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Marshall, S. G.
LREP Pennie & Edmonds
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 328
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . peptide salt, then suspending said peptide salt in a solution of a biodegradable polymeric material, converting said suspension into an **oil-in-water** type emulsion, and finally isolating the microspheres of biodegradable polymer after transfer of the **oil-in-water** emulsion into an excess of an aqueous medium.
SUMM . . . and EP-A-0058481 or U.S. Pat. No. 3,976,071 for the preparation of implants or of biodegradable porous matrices, based mainly on **polylactide** or on copolylactide-glycolide. These techniques make use of a prior dissolution in an organic solvent of the biodegradable polymer or. . .
SUMM . . . microcapsules or microspheres, make use of emulsification procedures, the most important step of such procedures being the obtention of an **oil-in-water** type emulsion from an organic solution of polymeric material and an aqueous solution of the peptide--see in this respect U.S.. . .
SUMM In a process using the formation of an emulsion of the **oil-in-water** type followed by its transfer into an aqueous medium, the invention enables, against all expectations, to overcome advantageously the short-commings. . .
SUMM As to the biodegradable polymeric material, the most commonly used are polymers such as a **polylactide**, a polyglycolide or a copolymer of lactic and glycolic acids.
SUMM . . . most generally of water complemented with an appropriate surfactant. The objective is to form rapidly a homogeneous emulsion of

the oil-in-water type, said aqueous medium functioning to provide the continuous phase. Various factors are to be considered when preparing such an. . .

CLM What is claimed is:

1. A sustained and controlled release composition consisting essentially of microspheres of biodegradable polymeric material which incorporate therein a water-insoluble salt of a medicamentous peptide substance having the formula (I): Ac-D-Nal-D-pClPhe-R^3 -Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2(I) wherein R^3 is D-Pal or D-Trp.

2. Composition according to claim 1, wherein the water-insoluble peptide is a pamoate, tannate, stearate or palmitate.

3. Composition according to claim 1, wherein the biodegradable polymeric material is a polylactide, a polyglycolide or a copolymer of lactic and glycolic acids.

5. Composition according to one of claims 1 in the form of microspheres of a 75:25 (molar %) copolymer of lactic and glycolic acids, including at least 5% in weight of the pamoate salt of a peptide of formula (I).

. . . release composition consisting essentially of microphores of a biodegradable polymeric material which incorporate therein a water-insoluble salt of a medicamentous peptide substance having the formula (I): Ac-D-Nal-D-pClPhe-R_3 -Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2(I) wherein R^3 is D-Pal or D-Trp, said composition prepared by process comprising the steps of: a) converting a water-soluble peptide salt of formula (I) into a water-insoluble peptide salt; b) suspending said water-insoluble peptide salt in an organic medium containing the biodegradable polymeric material in the dissolved state to afford an organic suspension; c). . . aqueous medium consisting essentially of water; d) transferring said emulsion into an excess of an aqueous medium; and e) separating microspheres thus obtained from the liquid phase, said microspheres containing a pharmaceutically effective amount between about 5-20% by weight of said water-insoluble peptide salt.

7. Composition according to claim 1, wherein before the transfer of the oil-in-water emulsion into an excess of aqueous medium, a partial evaporation of the organic solvent forming the oil phase is carried. .

.

8. Composition according to claim 1, wherein the water-insoluble peptide salt is a pamoate, a tannate, a stearate or a palmitate.

9. Composition according to one of claim 1, wherein the biodegradable polymeric material is a polylactide, a polyglycolide, or a copolymer of lactic and glycolic acids.

11. Process according to claim 6, wherein the water-insoluble peptide salt is present in the microspheres in an amount of from about 5% by weight.

13. A sustained and controlled release composition consisting essentially of microspheres of a biodegradable polymeric material which incorporate therein a water-insoluble salt of a medicamentous peptide substance, said water-insoluble salt having a water solubility less than or equal to 0.1 mg/ml at 25° C., said peptide substance having the formula (I): Ac-D-NAl-D-pClPhe-R^3 -Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2(I), wherein R^3 is D-Pal or D-Trp and said biodegradable polymeric material being a polylactide, a polyglycolide, or a copolymer of lactic and glycolic acids, said composition prepared by a process comprising the steps of: a) converting a water-soluble peptide salt of formula (I) into a water-insoluble peptide salt; b) suspending said water-insoluble peptide salt in an organic medium containing the biodegradable

polymeric material in the dissolved state to afford an organic suspension; c). . . essentially of water and a surfactant; d) transferring said emulsion into an excess of an aqueous medium; and e) separating **microspheres** thus obtained from the liquid phase, said **microspheres** containing a pharmaceutically effective amount between about 5-20% by weight of said water-insoluble **peptide** salt.

L3 ANSWER 12 OF 12 USPATFULL on STN

Full Text | Citing References

AN 95:77973 USPATFULL
TI Process for the preparation of microspheres made of a biodegradable polymeric material
IN Orsolini, Piero, Martigny, Switzerland
Heimgartner, Frederic, Martigny, Switzerland
PA Debio Recherche Pharmaceutique S.A., Martigny, Switzerland (non-U.S. corporation)
PI US 5445832 19950829
AI US 1992-915478 19920716 (7)
PRAI CH 1991-2178 19910722
DT Utility
FS Granted
EXNAM Primary Examiner: Warden, Jill; Assistant Examiner: Lukton, David
LREP Pennie & Edmonds
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 444
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . peptide salt, then suspending said peptide salt in a solution of a biodegradable polymeric material, converting said suspension into an **oil-in-water** type emulsion, and finally isolating the microspheres of biodegradable polymer after transfer of the **oil-in-water** emulsion into an excess of an aqueous medium.
SUMM . . . and EP-A-0058481 or U.S. Pat. No. 3976071 for the preparation of implants or of biodegradable porous matrices, based mainly on **polylactide** or on copolylactide-glycolide. These techniques make use of a prior dissolution in an organic solvent of the biodegradable polymer or. . .
SUMM . . . microcapsules or microspheres, make use of emulsification procedures, the most important step of such procedures being the obtention of an **oil-in-water** type emulsion from an organic solution of polymeric material and an aqueous solution of the peptide--see in this respect U.S.. . .
SUMM In a process using the formation of an emulsion of the **oil-in-water** type followed by its transfer into an aqueous medium, the invention enables, against all expectations, to overcome advantageously the shortcommings. . .
SUMM As to the biodegradable polymeric material, the most commonly used are polymers such as a **polylactide**, a polyglycolide, a copolymer of lactic and glycolic acids, a polyester such as a polyalkylene fumarate or succinate or further. . .
SUMM . . . most generally of water complemented with an appropriate surfactant. The objective is to form rapidly a homogeneous emulsion of the **oil-in-water** type, said aqueous medium functioning to provide the continuous phase. Various factors are to be considered when preparing such an. . .
CLM What is claimed is:
1. A process for preparing a composition for the sustained and controlled release of a medicamentous **peptide** substance, said medicamentous **peptide** substance being a natural or synthetic poly **peptide** comprising from about 3 to about 45 amino acids, said composition being obtained in the form of **microspheres** of a biodegradable polymeric organic material incorporating said medicamentous substance, comprising the steps of: (a) converting a water

soluble **peptide** or **peptide** salt into a corresponding water-insoluble **peptide** salt selected from the group consisting of the pamoate, stearate, and palmitate of said **peptide**; (b) suspending said water-insoluble **peptide** salt in an organic solvent containing a dissolved biodegradable polymeric organic material to form a suspension; (c) dispersing said organic. . . forms the continuous phase of the emulsion; (d) transferring said emulsion into an excess of an aqueous medium, and separating **microspheres** from the liquid phase.

. . . somatoststin, insulin, glucagon, auricular natriuretic factor (ANF), endorphin, a renin inhibitor, luteinizing hormone-releasing hormone (LHRH), growth hormone releasing hormone (GHRH), **peptide** T, their synthetic analogues and their synthetic homologues.

. . . according to one of claims 1 or 2 wherein the biodegradable polymeric material is selected from the group consisting of **polylactides**, polyglycolides, copolymers of lactic and glycolic acids, polyesters, polyalkylene fumarate, polyalkylene succinate, polyorthoesters, polyacetals and polyanhydrides.